STATISTICAL ANALYSIS PLAN

A PHASE 3, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY OF THE EFFICACY AND SAFETY OF APREMILAST (CC-10004) IN SUBJECTS WITH MILD TO MODERATE PLAQUE PSORIASIS

INVESTIGATIONAL PRODUCT (IP):	**Apremilast (CC-10004)**
PROTOCOL NUMBER:	**CC-10004-PSOR-022**
DATE FINAL:	**12MAR2020**

Prepared by:

Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

NCT Number: NCT03721172
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE	
SAP TITLE	Statistical Analysis Plan for a Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Apremilast (CC-10004) in Subjects with Mild to Moderate Plaque Psoriasis
SAP VERSION, DATE	Final, 2April2020
SAP AUTHOR	[redacted] Associate Director, Biostatistics [redacted] [redacted] Printed Name and Title Signature and Date
PROTOCOL TITLE	Phase 3, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of the Efficacy and Safety of Apremilast (CC-10004) in Subjects with Mild to Moderate Plaque Psoriasis
INVESTIGATIONAL PRODUCT	Apremilast (CC-10004)
PROTOCOL NUMBER	CC-10004-PSOR-022
PROTOCOL VERSION, DATE	Amendment 2, 21Nov2018
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.
Statistical Therapeutic Area Head Signature [redacted] Printed Name [redacted] Date [redacted]	
Lead Clinical Research Physician / Clinical Research Physician / Medical Affairs Physician Signature [redacted] Printed Name [redacted] Date [redacted]	
Lead Product Safety Physician / Medical Affairs Physician (if applicable) Signature [redacted] Printed Name [redacted] Date [redacted]	

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

AE	Adverse Event
ANCOVA	Analysis of Covariance (model)
ATC	Anatomical-Therapeutic-Chemical
BID	Twice Daily
BMI	Body Mass Index
BSA	Body Surface Area (%) Affected by Psoriasis
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF or eCRF	(electronic) Case Report Form
CRO	Contract Research Organization
CRP	Clinical Research Physician
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DAO	Data As Observed
DLQI	Dermatological Life Quality Index
EAIR	Exposure Adjusted Incidence Rate
HRQoL	Health-Related Quality of Life
IP	Investigational Product
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LS Mean	Least Squares Mean
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed-effect Model for Repeated Measures
NAPSI	Nail Psoriasis Severity Index

NRI	Non-responder Imputation
NRS	Numeric Rating Scale
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PG	Pharmacogenetic
PK	Pharmacokinetic
PP	Per-Protocol (population)
PT	Preferred Term
REML	Restricted Maximum Likelihood
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
ScPGA	Scalp Physician Global Assessment
SD	Standard Deviation
SE	Standard Error
SI	Standard International (unit)
sPGA	Static Physician Global Assessment
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
USA	United States of America
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol CC-10004-PSOR-022, "A phase 3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of apremilast (CC-10004) in subjects with mild to moderate plaque psoriasis".

After all subjects have completed or have been discontinued from the Double-blind Placebo-controlled Phase (Weeks 0 to 16), a Week 16 database restriction will be performed; the primary data analysis will be conducted and a Week 16 Clinical Study Report will be generated. No interim analysis is planned prior to this primary data analysis. At the end of the study, after all subjects have completed or have been discontinued from the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase, the final database lock and analysis will be performed and the final Clinical Study Report (CSR) will be generated.

No pharmacokinetic (PK) analyses will be done for this study. The details of the pharmacodynamic (PD) analyses except biomarker analysis for plasma proteins assessments will be specified in a separate PD analysis plan.

This SAP provides a more technical and detailed elaboration of the statistical analyses as outlined and/or specified in the study protocol amendment 2 dated 21Nov2018. The SAP will be finalized and signed prior to the unblinding of the Week 16 database. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.3 or higher.

3. STUDY OBJECTIVES STUDY OBJECTIVES

3.1. Primary Objective

- To evaluate the clinical efficacy of oral apremilast 30 mg twice daily (BID), compared to placebo, in subjects with mild to moderate plaque psoriasis during the 16-week Placebo-controlled Phase

3.2. Secondary Objectives

The secondary objectives are:

- To evaluate the safety and tolerability of apremilast 30 mg BID, compared with placebo, in subjects with mild to moderate plaque psoriasis
- To evaluate the effect of apremilast 30 mg BID compared with placebo on itch over the whole body caused by plaque psoriasis
- To evaluate the effect of apremilast 30 mg BID compared with placebo on Health-related Quality of Life (HRQoL)

3.3. Exploratory Objectives

The exploratory objectives are:

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 3, multicenter, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy and safety of apremilast (CC-10004) in subject with mild to moderate plaque psoriasis.

Approximately 574 subjects will be enrolled and randomized 1:1 to receive either apremilast 30 mg BID or placebo for the first 16 weeks. Subjects will be randomized based on a permuted block randomization using a centralized Interactive Response Technology (IRT). Randomization to apremilast arm or placebo arm will be stratified by baseline Static Physician Global Assessment (sPGA) score (mild [2] or moderate [3]). Approximately 30% of subjects with mild plaque psoriasis will be enrolled in the study.

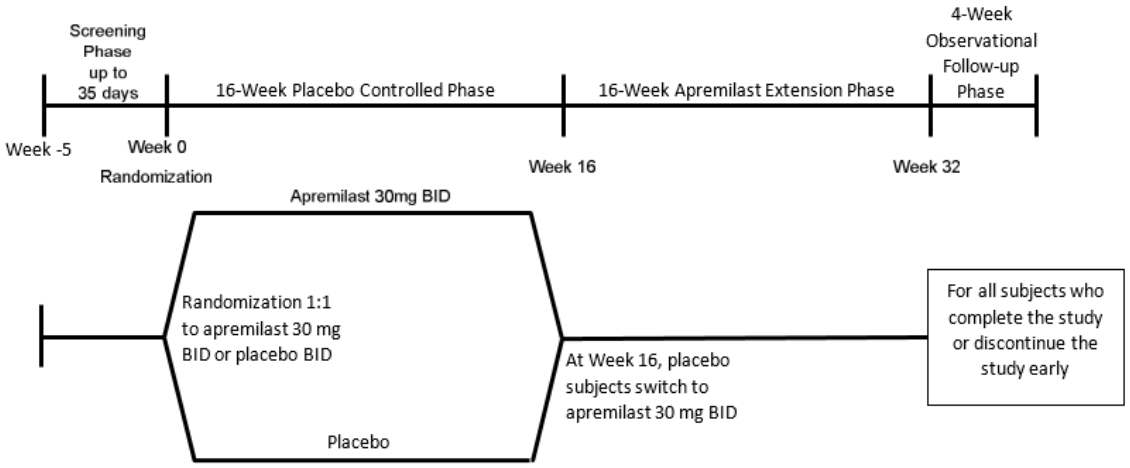
- Subjects randomized to the apremilast 30 mg BID treatment group will receive apremilast 30 mg tablets orally twice daily for the first 16 weeks
- Subjects randomized to the placebo treatment group will receive placebo tablets (identical in appearance to apremilast 30 mg tablets) orally twice daily for the first 16 weeks
- All subjects will receive apremilast 30 mg tablets orally twice daily after the Week 16 Visit through the end of the Apremilast Extension Phase of the study

The study will consist of four phases (Figure 1):

- Screening Phase – up to 35 days
- Double-blind Placebo-controlled Phase – Weeks 0-16
  - Subjects will be randomly assigned in a 1:1 ratio to either apremilast 30 mg BID or placebo.
- Apremilast Extension Phase – Weeks 16-32
  - All subjects will be switched to (or continue with) apremilast 30 mg BID. All subjects will maintain this dosing through Week 32.
- Observational Follow-up Phase – 4 weeks
  - Four-week Post-Treatment Observational Follow-up Phase for all subjects who complete the study or discontinue the study early

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed; the primary data analysis will be conducted and a Week 16 Clinical Study Report (CSR) will be generated. However, unblinded data will only be made available to select Sponsor and Contract Research Organization (CRO) team members involved with analysis of the data and preparation of the Week 16 CSR. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study, will remain blinded to treatment assignments until the final database lock at the conclusion of the study.

Figure 1: Study Design



4.2. Study Endpoints

The endpoints of the study are listed below.

4.2.1. Primary Endpoint

- Static PGA (sPGA) 0/1: Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16

4.2.2. Secondary Endpoints

- BSA-75: Proportion of subjects who improved ≥ 75% in BSA (BSA-75) from baseline at Week 16
- BSA: Change from baseline in affected BSA at Week 16
- PASI: Change from baseline in total PASI score at Week 16
- BSA ≤ 3%: Proportion of subjects who achieved BSA ≤ 3% for subjects with baseline BSA > 3% at Week 16
- Itch NRS: Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score at Week 16, among subjects with baseline whole body itch NRS ≥ 4
- ScPGA: Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16, among subjects with baseline ScPGA score ≥ 2
- DLQI: Change from baseline in DLQI total score at Week 16

4.2.3. Exploratory Efficacy Endpoints

[redacted]

4.2.4. Exploratory Pharmacokinetic Endpoints

Not applicable.

4.2.5. Exploratory Pharmacodynamics Endpoints

[redacted]

4.2.6. Safety Endpoints

Safety endpoints will include:

- Adverse events (AEs): Type, frequency, severity, seriousness, and relationship of AEs to IP
- Death
- Clinical laboratory evaluations
- Vital signs and weight
- Columbia Suicide Severity Rating Scale (C-SSRS)

4.2.7. Derivations of Efficacy Endpoints

The derivation of efficacy endpoints is described below in separate sections. Baseline definition for all efficacy endpoints is given in Section 5.3. Change from baseline is calculated as post-baseline visit value minus the baseline value. Percent change from baseline is defined as 100* Change from baseline/Baseline value (%). Handling of time points is described in Section 5.4.

4.2.7.1. Static Physician Global Assessment (sPGA)

The sPGA is the assessment of whole body psoriasis by the investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from clear (0), almost

clear (1), mild (2), moderate (3), to severe (4), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation.

The sPGA response at a post-baseline visit is defined as achieving sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline.

4.2.7.2. Body Surface Area (BSA)

BSA is a measurement of involved skin over the whole body. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand. The surface area of the whole body is made up of approximately 100 palms or "handprints" (each entire palmar surface or "handprint" equates to approximately 1% of total body surface area).

BSA scores will be presented with one digit after the decimal point. For post-baseline visits, BSA score change and percent change from baseline will be derived. BSA score percent change will be rounded to integers.

4.2.7.3. Psoriasis Area and Severity Index (PASI)

The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. Psoriasis Area and Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity. Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score. The PASI score will be set to missing if any severity score or degree of involvement is missing.

PASI scores will be presented with one digit after the decimal point. For post-baseline visits, PASI score change and percent change from baseline will be derived. PASI score percent change will be rounded to integers.

4.2.7.4. Whole Body Itch Numeric Rating Scale (NRS) Assessment

The whole body itch NRS assessment is a tool designed to measure the amount of whole body itch due to psoriasis by circling a number on a scale from 0 to 10. Subjects will be asked to assess their worst level whole body itch in the past 24 hours and select a number on a scale of 0 to 10, where "0" represents no itching, and "10" represents the worst itch imaginable.

For a post baseline visit, the whole body itch NRS response is defined as ≥ 4 points reduction (improvement) from baseline in the NRS score for subjects with baseline score 4 or higher. Change from baseline in the NRS score will also be derived.

4.2.7.5. Scalp Physician Global Assessment (ScPGA)

The ScPGA is a measurement of overall scalp involvement. The ScPGA is a 5-point scale that assesses three dimensions (Plaque Elevation, Scaling, and Erythema) on a scale of 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), to 4 (severe).

For a post baseline visit, the ScPGA response is defined as achieving ScPGA global assessment of 0 (clear) or 1 (almost clear) with at least a 2-point reduction from baseline among subjects with baseline ScPGA score ≥ 2. Change from baseline in the ScPGA score will also be derived.

4.2.7.6. Dermatology Life Quality Index (DLQI)

The DLQI was developed as a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease. The instrument contains 10 items dealing with the subject's skin. With the exception of Item Number 7, the subject responds on a four-point scale, ranging from "Very Much" (score 3) to "Not at All" or "Not relevant" (score 0). Item Number 7 is a multi-part item, the first part of which ascertains whether the subject's skin prevented them from working or studying (Yes or No, scores 3 or 0 respectively), and if "No," then the subject is asked how much of a problem the skin has been at work or study over the past week, with response alternatives being "A lot," "A little," or "Not at all" (scores 2, 1, or 0 respectively). The DLQI total score is derived by summing all item scores, which has a possible range of 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best.

If one of the 10 items is left unanswered, it is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If two or more of the ten items are left unanswered, DLQI total score will be left missing. When using sub-scales, if the answer to one item in a sub-scale is missing, the score is set to missing for that sub-scale.

DLQI total score and change from baseline will be derived.

4.2.8 Derivations of Safety Endpoints

Baseline definition for all safety endpoints is given in Section 5.3. Change from baseline is calculated as post-baseline visit value minus the baseline value. Handling of time points is described in Section 5.4.

4.2.8.1. Treatment-emergent Adverse Event

An AE is a treatment-emergent AE (TEAE) if the AE start date is

- On or after the date of the first dose of investigational product (IP) and no later than 28 days after the last dose of IP for subjects who have completed study treatment or have discontinued early by the time of database cut, or
- On or after the date of the first dose of IP for subjects who are ongoing with study treatment at the time of database cut.

If the treatment-emergent status of an AE is unclear due to a missing/incomplete start date, it will always be considered treatment-emergent, unless shown otherwise by data. Date imputation rules for missing AE start dates are described in Appendix A1.

Adverse event started more than 28 days after the last dose of IP will not be considered as a treatment-emergent AE.

4.2.8.2. Treatment-emergent Adverse Event Leading to Drug Withdrawal, Drug Interruption, or Death, and Drug-related Treatment-emergent Adverse Event

A TEAE leading to drug withdrawal is a TEAE for which the investigator indicates that the action taken with respect to IP is withdrawn permanently. A TEAE leading to drug interruption is a TEAE for which the investigator indicates that the action taken with respect to IP is interrupted. A TEAE leading to death is a TEAE for which the outcome is fatal. Relationship to IP is based on the investigator's causality judgment; that is, a drug-related AE is an AE indicated by the investigator to have a suspected relationship to IP.

4.2.8.3. Vital Signs and Weight

Vital signs and weight endpoints include:

- Observed value and change from baseline over time in vital signs (temperature, pulse, and blood pressure)
- Observed value, change and percent change from baseline over time in weight
- Shifts from baseline to post-baseline timepoints and to the worst post-baseline value in terms of normal/abnormal in pulse and blood pressure (normal ranges are defined as: 60-100 beats/minute for pulse, 90-140 mmHg for systolic blood pressure, and 60-90 mmHg for diastolic blood pressure)

4.2.8.4. Clinical Laboratory Evaluations

Laboratory evaluations include:

- Observed value and change from baseline over time in hematology and serum chemistry parameters
- Laboratory marked abnormalities (see Appendix A2)
- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal (low or high) in hematology and serum chemistry parameters

4.2.9 Derivations of Pharmacokinetic Endpoints

Not applicable.

4.2.10 Derivations of Pharmacodynamic Endpoints

Blood samples will be collected at Visit 2 (Baseline) and Week 16. Plasma proteins will be evaluated, such as but not limited to: IL-17A, IL-17F, and IL-22, as well as other markers for psoriasis and the mechanism of action for apremilast. The endpoints include observed values, changes and percent changes from baseline in biomarkers.

Derivations of rest of the pharmacodynamic endpoints including peripheral blood RNA gene expression, pharmacogenetic assessment and microbiome skin swab data will be specified in a PD analysis plan separately.

4.3. Randomization, Stratification, and Blinding

Approximately 574 subjects will be enrolled and randomized 1:1 to receive either apremilast 30 mg BID or placebo for the first 16 weeks. Subjects will be randomized based on a permuted block randomization using a centralized Interactive Response Technology (IRT). Randomization to apremilast arm or placebo arm will be stratified by baseline sPGA score (mild [2] or moderate [3]). Approximately 30% of subjects will be with sPGA score of mild (2) and approximately 70% of subjects will be with sPGA score of moderate (3). The IRT system will monitor the total enrollment of each stratum and screening will close once the approximate percentages are reached.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed; the primary data analysis will be conducted and a Week 16 CSR will be generated. However, unblinded data will only be made available to select CRO team members involved with analysis of the data and preparation of the Week 16 CSR. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study will remain blinded to treatment assignments until the final database lock at the conclusion of the study.

4.4. Sample Size Determination

The sample size estimation is based on the results of the Phase 3 and 4 studies with apremilast. With a total of approximately 574 subjects and a randomization ratio of 1:1, the study will randomize approximately 287 subjects to apremilast 30 mg BID and 287 subjects to placebo. This sample size will provide more than 90% power to detect a 15% difference between the two treatment groups for the primary endpoint at a two-sided significance level of 0.05. The calculation is based on a chi-square test assuming 15% response rate for placebo and adjusting for a 20% dropout rate.

5. ANALYSIS PHASES OR PERIODS, DEFINITION OF ANALYSIS POPULATIONS, BASELINE AND TIME POINTS

5.1. Analysis Phases or Periods

For efficacy analysis, different phases will be used. For safety analysis, Placebo-controlled Phase and Apremilast-exposure Period will be used.

5.1.1. Analysis Phases

Per protocol specification, data summary and analysis will be provided for the following phases.

- Placebo-controlled Phase – Weeks 0 to 16

  This phase starts on the day of randomization (Week 0/Visit 2), and stops on either: (1) the day the first IP for the next phase is dispensed at Week 16/Visit 7; or (2) the day of the discontinuation visit if the subject discontinued prior to or at Week 16/Visit 7; or (3) the last known study day if the subject is lost to follow-up prior to Week 16/Visit 7 during the phase.

  For safety analysis in subjects who continued treatment in Apremilast Extension Phase (Weeks 16 to 32), the phase stopped one day prior to the first dose date in Apremilast Extension Phase.

  For the analysis of measured (ie, visit-based) safety data (ie, labs, vital signs, and ECG), this period is exclusive of the date of the first dose of IP and inclusive of the date of the first Week 16 dose of Apremilast.

  At the time of the Week 16 analysis, if the date of the first Week 16 dose of Apremilast (derived from the Study Drug Exposure eCRF which may not be entered by sites until the next visit after Week 16) is not yet available for subjects with Apremilast dispensed at Week 16 and on or before the (possibly derived) date of the last dose of IP as of the time of analysis (ie, no evidence that the subject has discontinued without receiving at least one dose of Apremilast after Week 16), the date of Apremilast dispensing at Week 16 will replace the date of the first Week 16 dose of Apremilast in the above definition for these subjects.

- Apremilast Extension Phase – Weeks 16 to 32

  This phase starts on the day after the first IP is dispensed for the phase at Week 16/Visit 7, and stops on either: (1) the day of Week 32/Visit 10; or (2) the day of the discontinuation visit if the subject discontinued prior to or at Week 32/Visit 10; or (3) the last known study day if the subject is lost to follow-up prior to Week 32/Visit 10 during the phase.

  For safety analysis, the phase started at the first dose date in the phase and ended at the last dose date + 1.

- Observational Follow-up Phase – 4 weeks

Subjects who complete the study or discontinue the study early, will be followed up for 28 days after the last dose of IP.

5.1.2. Apremilast-exposure Period for Safety Analysis

Apremilast-exposure Period will be used for safety analyses.

- Apremilast-exposure Period:

  This period starts on the date of either: (1) the first dose of IP following randomization (Week 0/Visit 2) for subjects who are treated with apremilast from Week 0; or (2) the first dose of IP from the IP dispensed at Week16/Visit 7 for subjects who were originally treated with placebo and are treated with apremilast at Week 16.

  This period stops on either: (1) data cut-off date; or (2) the end of the study.

5.1.3. Treatment Arms in Analysis Phases

In general, the treatment arms used in the analyses and summaries in each phase are described below in this section unless otherwise specified.

- Placebo-controlled Phase (Weeks 0 to 16)
  - Placebo
  - Apremilast 30 mg BID
  - Total (optional, not for the efficacy analysis)

- Apremilast Extension Phase (Weeks 16 to 32)
  Subjects who entered the extension phase will be included in analysis, i.e, subjects who were initially randomized to apremilast and continued at Week 16 or who were initially randomized to placebo and switched to apremilast at Week 16.
  - Placebo/30 mg BID
  - 30 mg BID/30 mg BID
  - Total

- Apremilast-exposure Period
  Subjects who are treated with at least one dose of apremilast will be included here, which includes all subjects who are randomized to (at Week 0/Visit 2) or switched to (at Week 16/Visit 7) apremilast, and receive at least one dose of apremilast after randomization or Week 16.
  - Placebo/30 mg BID
  - 30 mg BID as Initiated
  - 30 mg BID as Treated

- Observational Follow-up Phase (4 weeks)
  For subjects who entered Follow-up Phase from Placebo-controlled Phase, summaries will be provided by their initial treatment arm:

- Placebo
- 30 mg BID

For subjects who entered Follow-up Phase from Apremilast Extension Phase, summaries will be provided by their treatment sequence:

- Placebo/30 mg BID
- 30 mg BID/30 mg BID

5.2. Definition of analysis populations

5.2.1. Intent-to-treat Population

The intent-to-treat (ITT) population will consist of all subjects who are randomized regardless of whether or not the subject received IP. Subjects will be included in the treatment group to which they are randomized.

5.2.2. Per-protocol Population

The per protocol (PP) population will consist of all subjects included in the ITT population who receive at least one dose of IP, have both baseline and at least one post-treatment sPGA assessment, and have no important protocol deviations which may affect efficacy assessments in the Placebo-controlled Phase.

5.2.3. Safety Population

The safety population will consist of all subjects who are randomized and received at least one dose of investigational product (IP). Subjects will be included in the treatment group corresponding to the IP they actually received (apremilast or placebo) for the analyses and summaries using the safety population.

5.3. Baseline Definitions

For efficacy analysis and summary of baseline disease characteristics data, baseline is defined as the last value measured prior to or at the randomization date.

For safety analyses in the Placebo-controlled Phase, baseline will be relative to the first dose date following randomization at Week 0. It is the last value measured prior to or on the day of the first dose of IP.

For safety analyses in Apremilast Exposure Period, baseline will be relative to the first apremilast dose date at Week 0 for subjects initially randomized to apremilast or Week 16 for subjects initially randomized to placebo and switched to apremilast in the Extension Phase. It is the last value measured prior to or at the first apremilast dose date.

5.4. Time Points

Time points in all analyses are based on the remapped visits/study weeks using the following visit mapping algorithm, which may or may not be the same as the visits/study weeks as recorded in the database.

All visit-based data, except for those with the recorded visit being a follow-up visit, will be assigned to analysis visits based on study day (the date of assessment/collection relative to the reference date) and the defined analysis visit windows (Table 2), rather than the recorded visit. The only exception is that data with the recorded visit being a follow-up visit will be assigned to the analysis visit corresponding to the follow-up visit.

Table 2: Table for Visit Mapping

Analysis Visit	**Target Day**	**Visit Window**
Week 0 (Baseline)	1	≤ 1
Placebo-controlled Phase		
Week 2	15	2 – 21
Week 4	29	22 – 42
Week 8	57	43 – 70
Week 12	85	71 – 98
Week 16	113	99 – End of Phase
Apremilast Extension Phase		
Week 20	141	Start of Phase – 154
Week 24	169	155 – 196
Week 32	225	197 – End of Phase

Note: Target day and visit window are relative to the date of Visit 2/Week 0 (Day 1) randomization date. For efficacy and safety analysis, definitions for start or end dates for a phase or period are specified in Section 5.1 and Baselines are specified in Section 5.3.

Time points in the analyses or summaries of efficacy data over time include the scheduled study weeks per protocol, the end of a study phase, and the observational follow-up visit when applicable. It is possible that multiple assessment values will fall into the same visit window. The following rule may be used to select the unique value for that analysis visit:

1. Among all assessments in the same visit window for the analysis visit, select the value with the assessment date closest to the target day of the analysis visit;
2. If the relative days from 2 assessments are equally close to, but on different sides of the target day, then the latter assessment will be used for that analysis visit;

3. If multiple assessments are available on the same relative day, the duplicated values will be suppressed; otherwise, the highest value of these assessments will be used for that relative day.

For the Apremilast-exposure Period, the scheduled study weeks for placebo subjects who are treated with apremilast 30 mg BID at Week 16/Visit 7 are shown below for summaries of safety data (laboratory parameters, vital signs, etc) over time.

Table 3: Analysis Visit for Placebo Subjects Who Are Treated with Apremilast 30 mg BID after Week 16 in the Apremilast-exposure Period

Original Visit	**Analysis Visit**
Week 16	Week 0 (Baseline)
Week 20	Week 4
Week 24	Week 8
Week 32	Week 16

6. STATISTICAL METHODOLOGY FOR EFFICACY

6.1. General Approaches to Efficacy Analysis

The intent-to-treat principle will be used in statistical analyses for efficacy endpoints. For the Placebo-controlled Phase (Weeks 0-16), efficacy evaluations will be conducted using the intent-to-treat (ITT) population defined as all randomized subjects. Statistical comparisons will be made between the two treatment arms (placebo or apremilast). For the Apremilast Extension Phase (Weeks 16-32), efficacy evaluations will be conducted using subjects who entered the phase from both treatment arms.

Descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) will be presented for appropriate endpoints at specified time points. Specifically, for continuous variables, descriptive statistics for assessment values and change (plus percentage change when specified) from baseline will be provided. Binary variables will be summarized with frequency tabulations.

Statistical comparisons will be made between placebo arm and apremilast arm; the null hypothesis is that the effects of the two treatment arms (i.e., placebo vs. apremilast) have no difference. Statistical tests will be at the two-sided 0.05 significance level and the corresponding p-values and two-sided 95% confidence intervals (CIs) will be reported.

In the data as observed (DAO) analyses, only subjects with sufficient data at the time point under consideration will be included.

6.2. Multiplicity Adjustment

The primary and secondary efficacy endpoints will be hierarchically ranked for testing to control the overall type I error rate in claiming statistical significance at the two-sided 0.05 significance level. Specifically, for the primary efficacy endpoint (sPGA response at Week 16), if the two-sided p-value from the comparison between apremilast arm and placebo arm is below 0.05, the outcome will be considered statistically significant and apremilast will be declared effective. For any secondary endpoint, statistical significance will be claimed only if its two-sided p-value is below 0.05 and tests for the primary endpoint and all previous secondary endpoints are significant at the two-sided 0.05 level. The proposed test sequence for the primary and secondary efficacy endpoints is listed as the following:

- Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16
- Proportion of subjects who improved ≥ 75% in BSA (BSA-75) from baseline at Week 16
- Change from baseline in affected BSA at Week 16
- Change from baseline in total PASI score at Week 16
- Proportion of subjects who achieved BSA ≤ 3% for subjects with baseline BSA > 3% at Week 16
- Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score at Week 16, among subjects with baseline whole body itch NRS ≥ 4

- Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16, among subjects with baseline ScPGA score ≥2
- Change from baseline in DLQI total score at Week 16

6.3. Analyses of the Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects who achieve sPGA response at Week 16 (defined as sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16).

The primary endpoint will be analyzed using the CMH (Cochran–Mantel–Haenszel) test adjusting for the stratification factor at randomization (mild vs. moderate sPGA). The two-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% CIs using a normal approximation to the weighted average will be provided.

Missing values at Week 16 for this endpoint will be imputed using the multiple imputation (MI) method (SAS Institute Inc. 2011) based on similar subjects who remained in the study as the primary method. The SAS procedure MI will be used to impute missing sPGA scores at the scheduled analysis visits in the Placebo-controlled Phase (Weeks 0-16) to create M=50 complete datasets. The missing data patterns will be checked at the scheduled analysis visits, i.e., Baseline (Week 0), and Weeks 2, 4, 8, 12 and 16. If there are non-monotone missing patterns, two separate imputation procedures will be used to complete the imputation process.

In the first step, the Markov Chain Monte Carlo (MCMC) method will be used with a single chain to impute missing scores by treatment and stratification factor to create M=50 imputed datasets with monotone missing patterns. In case there are convergence issues, a simpler model will be used to impute the missing scores by treatment, with further simplification by dropping both treatment and stratification factor from the imputation model if necessary. The seed will be set to 17813721. The imputed scores will be rounded to the nearest integer. The minimum and the maximum values for imputation will be 0 and 4, which correspond to the lowest and the highest sPGA scores.

In the second step, the predictive mean matching method will be used to impute the remaining missing scores for the 50 datasets with monotone missing patterns. The imputation procedure will use the monotone statement to create one complete dataset for each of the monotone datasets from the first step, and the variables will include treatment arm, stratification factor, and sPGA scores at scheduled analysis visits from baseline to Week 16. The seed will be set to 55218163. The number of closest observations to be used in the selection will be set to 2.

After the completion of imputation, sPGA response at Week 16 will be derived based on both observed and imputed scores. The same CMH method will be used to analyze the 50 complete datasets. The SAS procedure MIANALYZE will be used to combine the results for the statistical inferences.

Sensitivity analysis will be conducted to account for missing data using the NRI (Non-responder Imputation) method and the tipping point analyses.

By NRI, subjects who have insufficient data for response determination for the time point under consideration will be considered non-responders for that time point. Insufficient data, including missing data at baseline (if the binary endpoint assesses change from baseline) or a post-baseline time point, will be determined after the handling of time points as described in Section 5.4.

For the tipping point analyses, let M1 and M2 be the total number of subjects with missing data of primary endpoint in Apremilast and Placebo. There are overall (M1+1)*(M2 +1) possible ways for imputing missing data as responders or non-responders in statistical analysis, ranging from imputing all missing values as non-responders to imputing all missing values as responders in each of the two arms. For each of the (M1+1)*(M2 +1) different imputation patterns, the Chi-square test will be used for testing statistical significance and the output will be plotted in a rectangle for inspection. The staircase region that separates significant and non-significant outcomes forms the tipping-point boundary.

A supplementary analysis using the PP population will also be performed.

The primary endpoint will be assessed for site effect as specified in Section 6.7.

6.4. Analyses of the Secondary Efficacy Endpoints

For the analyses of the secondary efficacy endpoints, the two-sided p-values and two-sided 95% CIs will be reported for the treatment difference between placebo arm and apremilast arm. Details for multiplicity adjustment are described in Section 6.2.

6.4.1. Binary Variables

The binary variables for secondary endpoints include the following:

- Proportion of subjects who improved ≥ 75% in BSA (BSA-75) from baseline at Week 16
- Proportion of subjects who achieved BSA ≤ 3% for subjects with baseline BSA > 3% at Week 16
- Proportion of subjects with ≥4-point reduction (improvement) from baseline in the whole body itch NRS score at Week 16, among subjects with baseline whole body itch NRS ≥ 4
- Proportion of subjects with ScPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16, among subjects with baseline ScPGA score ≥ 2

For these binary endpoints, the treatment difference between apremilast arm and placebo arm will be compared using CMH test adjusting for the stratification factor at randomization. The two-sided p-values from the CMH test, the adjusted treatment difference in proportion using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% CIs using a normal approximation to the weighted average will be provided.

Missing values will be imputed using the similar MI method as the primary endpoint, with sensitivity analysis using the NRI method as described in section 6.3.

Further, analyses of the following secondary endpoints will be performed for the subjects with baseline sPGA =2 (mild psoriasis) and sPGA = 3 (moderate psoriasis):

- Proportion of subjects who improved ≥ 75% in BSA (BSA-75) from baseline at Week 16
- Proportion of subjects who achieved BSA ≤ 3% for subjects with baseline BSA > 3% at Week 16
- Proportion of subjects who achieved BSA ≤ 1% for subjects with baseline BSA > 1% at Week 16

The treatment difference between apremilast arm and placebo arm will be compared using Chi-squared test. The two-sided p-values from the Chi-squared test, the treatment difference in proportion, along with the associated two-sided 95% CIs will be provided.

6.4.2. Continuous Variables

The continuous variables for secondary endpoints include the following:

- Change from baseline in affected BSA at Week 16
- Change from baseline in total PASI score at Week 16
- Change from baseline in DLQI total score at Week 16

The continuous efficacy endpoints will be analyzed based on the ITT population using a mixed-effect model for repeated measures (MMRM) as the primary method. The MMRM model will use the change from baseline as the response variable and include treatment group, visit time, treatment-by-time interaction, and stratification factor as fixed effects, and the baseline value as a covariate. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted maximum likelihood (REML) to make proper statistical inference. Within-group least-squares (LS) means and the associated SEs and 2-sided 95% CIs, treatment differences in LS means and the associated 2-sided 95% CIs and 2-sided p-values will be derived from the MMRM model.

The continuous efficacy endpoints will also be analyzed based on the baseline sPGA categories (sPGA = 2 and sPGA =3) using the similar analysis method specified for the ITT population. For the subjects with baseline sPGA = 2 (mild psoriasis) and sPGA = 3 (moderate psoriasis), the MMRM model will use the change from baseline as the response variable and include treatment group, visit time, and treatment-by-time interaction as fixed effects, and the baseline value as a covariate.

6.5. Analyses of Exploratory Efficacy Endpoints

[redacted]

[redacted]

6.5.1. NAPSI

The endpoints include the following:

- Change from baseline in NAPSI at Week 16 and Week 32
- Proportion of subjects with NAPSI score of 0 at Week 16 and Week 32

For summary and analyses, only subjects with nail psoriasis at baseline will be included.

6.5.2. BSA

The endpoint is proportion of subjects who achieved BSA ≤ 1% at Week 16.

6.6. Subgroup Analysis

Subgroup analysis will be carried out for sPGA response at Week 16 in the Placebo-controlled Phase based upon baseline demographics and disease characteristics. Summary and analysis will be based on ITT population and missing values will be imputed using MI method. Treatment difference of response rates will be reported with two-sided 95% CI.

Forest plots for the treatment differences in proportions by subgroup will be provided.

The following subgroup variables will be used:

- Baseline sPGA score: 2 (mild), 3 (moderate)
- Sex (Male, Female)
- Race (White, Non-white)
- Age category (<65 years, ≥ 65 years)
- Alcohol usage (Yes, No)
- Tobacco usage (Current user, Past user, Never used)
- Baseline weight category < 70, ≥ 70 to < 85, ≥ 85 to < 100, ≥100 kg)
- Baseline BMI category < 25, ≥25 to < 30, ≥ 30 to < 35, ≥ 35 to < 40, ≥ 40 kg/m^2)
- Duration of plaque psoriasis categories (< 10, ≥ 10 to < 20, ≥ 20 years)

- Geographical region (USA, Canada)
- Baseline PASI score category (≤7, >7)
- Baseline BSA (%) category (≤5, >5)
- Prior conventional systemic therapies (Used or Never used)
- Prior phototherapies (Used or Never used)

6.7. Assessing Study Site Effect

This study is a multicenter study and planned to have 65 study sites to enroll 574 subjects. A single site may not have sufficient number of subjects to allow meaningful within-site analysis if treatment effects stratified by baseline sPGA score; therefore, study sites effect will be assessed by pooling sites on geographic basis to help interpret the results.

In pooling sites for analysis, the minimum cell size of 5 randomized subjects per treatment arm (placebo arm or apremilast arm) per stratum of baseline sPGA score (mild [2] or moderate [3]) will be used. The pooling strategy is described as follows: 1) Sites will be pooled within each country (USA or Canada) according to their rank based on site-specific sample size, starting with the smallest sites; i.e., within a country, the smallest sites will first be pooled until the pooled site has a minimum cell size of 5 for each of the four cells. 2) The remaining un-pooled sites will then be pooled within the country with the smallest pooled site. 3) In the rare case that all sites pooled together in a country does not satisfy the above condition (a minimum cell size of 5 for each of the four cells), all sites in the country will be pooled together with the smallest pooled site of the other country.

Sites will be pooled together as described above in order to assess the site effect and site by treatment interaction on the primary efficacy endpoint listed below.

- Proportion of subjects with an sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Week 16

For the pooled sites, summary and analyses will be based on ITT population using MI imputation for missing values. Study site effect will be assessed for the primary endpoint by stratifying the analysis based on pooled site in addition to the stratification factor at randomization and examining whether the treatment differences adjusted for both stratification factor and pooled site are consistent with those from the primary analysis.

In addition, the consistency of the treatment effect across individual study sites (or pooled sites) will be assessed by performing a subgroup-type analysis with respect to the endpoints, with individual study sites (or pooled sites) treated as subgroups. Listings of response rates will be provided by individual study site and by pooled site. The treatment difference for each of the individual study sites (or pooled sites) will be reviewed to determine the effect among the individual study sites (or pooled sites).

6.8. Interim Analysis

No interim analysis will be conducted.

After all subjects have completed the Week 16 Visit (or discontinued from the study), a Week 16 database restriction will be performed; the primary data analysis will be conducted. However, unblinded data will only be made available to selected Sponsor and CRO team members involved with analysis of the data and preparation of the Week 16 Clinical Study Report. All other Sponsor, site, and CRO personnel directly involved with the conduct of the study will remain blinded to treatment assignments until the final database lock at the conclusion of the study. At the end of the study, after all subjects have completed or have been discontinued from the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase, the final analysis will be performed and a final CSR will be generated.

6.9. Analysis of Pharmacokinetic Endpoints

Not applicable.

6.10. Analysis of Pharmacodynamic Endpoints

Biomarker analysis for plasma proteins assessments will be conducted to explore the effects of apremilast on concentrations of a select set of interleukins and cytokines and the relationship between biomarker concentrations and clinical efficacy of apremilast. Proteins will be evaluated, such as but not limited to: IL-17A, IL-17F, and IL-22, as well as other biomarkers for psoriasis and the mechanism of action for apremilast.

Biomarker analysis will be conducted based on the Biomarker subset, which includes all subjects who are randomized and receive at least one dose of IP, have a baseline value and at least one post-baseline value for any biomarker of plasma proteins.

In the biomarker analysis, the endpoints (biomarkers) will be summarized at both baseline and Week 16. Observed values, changes and percent changes from baseline in biomarkers will be summarized. At Week 16 of the above DAO summaries, distribution-free 2-sided 95% CIs for medians using the binomial distribution will be provided for change and percent change from baseline. P-values for testing within-group change and percent change from baseline (against no change) will be calculated by the Wilcoxon signed-rank test.

At Week 16, between-group differences in change and percent change from baseline will also be estimated using the Hodges-Lehmann estimate of location shift and its asymptotic (or exact where appropriate) 2-sided 95% CI based on the Wilcoxon rank-sum test. P-values for the between-group differences (between apremilast and placebo) in change and percent change will be calculated by a nonparametric method using an ANCOVA model on rank-transformed data. The model will use the van der Waerden normal score of the change or percent change from baseline as the response variable, and include treatment group and randomization stratification factors as factors, and the van der Waerden normal score of the baseline value as a covariate.

An association between the primary efficacy endpoint, sPGA response at Week 16, and the biomarkers (IL-17A, IL-17F, IL-22) will be explored. The association will be explored by a logistic regression of the sPGA response on the biomarker (the absolute value, change from baseline, or percent change from baseline), treatment group, the biomarker-by-treatment group interaction, randomization stratification factors, and baseline biomarker. The odds ratio, 2-sided 95% CI, and 2-sided p-value associated with the biomarker for each treatment group, as well as the 2-sided p-value for the biomarker-by-treatment group interaction will be calculated from this model. The common odds ratio, 2-sided 95% CI, and 2-sided p-value associated with the biomarker across the overall data will also be calculated from a similar model without the biomarker-by-treatment group interaction; these results are meaningful when there is no evidence of the biomarker-by-treatment group interaction ($p > 0.1000$). In addition, Pearson and Spearman point-biserial partial correlation coefficients, controlling for randomization stratification factors, and baseline biomarker, will be provided for each treatment group and across the overall data (the latter will additionally control for treatment group), along with the associated 2-sided 95% CI and 2-sided p-value. All tests are not adjusted by multiplicity. The analyses will be performed with missing data for biomarkers and sPGA responses handled in DAO (see Section 6.1 for missing data handling).

A listing of biomarker values for subjects in Biomarker subset will be provided. For each biomarker, a bar chart for percent change from baseline at Week 16 (Mean ± standard error of the mean), by treatment group, will be provided. An asterisk will be added to indicate significant treatment differences between APR 30 BID and placebo groups at Week 16 (DAO).

Pharmacodynamic peripheral blood RNA gene expression, pharmacogenetic assessment and microbiome skin swab data will be documented in a separate PD analysis plan.

7. SUMMARY OF SUBJECT DISPOSITION

The number of subjects screened, the number and percentage of subjects randomized (as recorded in the IVRS database) will be summarized. The failed inclusion/exclusion criteria of subjects who were screened and not randomized will be included in the summary. The above percentages will be based on the number of subjects screened.

The number and percentage of subjects randomized will be tabulated by treatment arm, study site, and country. The percentages will be based on the number of subjects randomized.

Subject disposition will be provided by treatment arm and phase:

- Placebo-controlled Phase – Weeks 0 to 16

  Summary will be based on subjects who are randomized. Tabulation of subjects included in the ITT, PP, and Safety populations, subjects who completed and entered the next phase (Weeks 16 to 32), completed but did not enter the next phase, and discontinued early will be provided. The primary reasons for early discontinuation will also be tabulated. Subjects who complete and entered the next phase include subjects who have IP dispensed at Week 16/Visit 7, subjects who completed but did not enter the next phase include subjects who have either a Week 16 visit or a termination visit no earlier than the Week 16 visit window, and discontinued early subjects include those who discontinued prior to the Week 16 visit window.

- Apremilast Extension Phase – Weeks 16 to 32

  Summary will be based on subjects who entered the Apremilast Extension Phase, i.e., who had IP dispensed for the Phase. Subjects who entered the phase, took at least one dose of IP, completed, discontinued early, and primary reason for discontinuation will be provided.

- Observational Follow-up Phase (4 weeks)

  Summary will include subjects who entered Follow-up Phase. Subjects who entered the phase, completed, discontinued early, and primary reason for discontinuation will be provided.

Primary reasons for discontinuation in the Placebo-controlled, Apremilast Extension and Follow-up phases collected on the Disposition eCRF pages will be summarized with the following categories:

- Death
- AEs
- Pregnancy
- Lack of efficacy
- Non-compliance with study drug
- Lost to follow-up
- Protocol deviation

- Physician decision
- Study terminated by sponsor
- Withdrawal by subject
- Other

Listings will be provided for randomized subjects who early discontinued during the treatment period with primary reason for discontinuation. Listing of subjects excluded from PP population, with the reasons for exclusions, will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Summaries for the demographics, baseline characteristics, prior medication/procedure, and concomitant medications/procedure will be presented by treatment group and overall for the ITT population, as well as for the mild psoriasis subjects (defined as baseline sPGA =2) and moderate psoriasis subjects (defined as baseline sPGA =3). Subject data listings will also be provided.

8.1. Demographics

Summary statistics will be provided for the following continuous variables:

- Age (years)
- Weight (kg)
- Height (cm)
- Baseline Body Mass Index (BMI; kg/m^2)

Number and percentage will be provided for the following categorical variables:

- Sex (Male, Female)
- Age category (< 65, ≥ 65 years; < 40, ≥ 40 to < 65, ≥ 65 to < 75, ≥ 75 to < 85, ≥ 85 years)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Not Collected or Unknown)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown)
- Baseline weight category (< 70, ≥ 70 to < 85, ≥ 85 to < 100, ≥100 kg)
- Baseline BMI category (< 25, ≥25 to < 30, ≥ 30 to < 35, ≥ 35 to < 40, ≥ 40 kg/m^2)
- Geographical region (USA, Canada)
- Alcohol usage (Yes, No)
- Tobacco usage (Current user, Past user, Never used)

8.2. Baseline or Disease Characteristics

Baseline clinical characteristics will be summarized descriptively by treatment group, which will include the following:

- Duration of plaque psoriasis (from date of diagnosis to the date of informed consent; year, presented one digit after the decimal point)
- Duration of plaque psoriasis categories (< 10, ≥ 10 to < 20, ≥ 20 years)
- Baseline sPGA score: Mild (2), Moderate (3)
- Baseline psoriatic involved BSA (%)

- Baseline BSA (%) category (≤5%, >5%)
- Baseline PASI score
- Baseline PASI score category (≤7, >7)
- Baseline DLQI total score
- Baseline whole body itch NRS
- Baseline whole body itch NRS category (0 to 4, 5 to 10, ≥ 4)
- Number of prior phototherapies
- Number of prior biologic therapies
- Number of prior conventional systemic therapies
- Number of prior systemic therapies
- Number of failed prior phototherapies for subjects who had prior phototherapies
- Number of failed prior conventional systemic therapies for subjects who had prior conventional systemic therapies
- Number of failed prior systemic therapies for subjects who had prior systemic therapies

8.3. Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. A frequency summary (counts and percentage) of medical history will be presented by treatment group, system organ class (SOC), and preferred term (PT) for ITT population. A listing of medical history will be provided for the ITT population.

8.4. Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. Frequency summaries of prior and concomitant procedures will be provided for the safety population by treatment group, SOC, and PT.

Prior procedures are defined as those started before the first dose of IP. A concomitant procedure is defined similarly as a TEAE. Concomitant procedures will be summarized for (1) Placebo-controlled Phase (Weeks 0 to16), (2) Apremilast Extension Phase (Weeks 16 to 32).

8.5. Prior and Concomitant Medications

Prior and concomitant medication will be coded using the Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHO DD version March 2018 or higher). Prior medications will be summarized by treatment group (and overall), ATC2 level, and preferred name for the ITT population. Concomitant medications will be

summarized by treatment group, ATC2 level, and preferred name for the placebo-controlled phase for the safety population, and for the Apremilast-exposure periods for the Apremilast 30 mg BID subjects as treated population. Frequency summaries will be provided by treatment group, ATC 2 level, and standardized medication name for the safety population.

Prior medications are defined as those started before the first dose of IP. Prior medications that continue after the first dose of IP will also be reported as concomitant medications.

For each of the treatment phases, Concomitant medications are defined as non-study medications started during the phase, or non-study medications started before the phase and ended or remained ongoing during the phase. The treatment phase for concomitant medications will start on the first dose date and end on the last dose date.

Medications in the Follow-up Phase will include those medications started after the date of last dose of investigational product.

Summaries will be provided for prior psoriasis medications and prior medications, as well as for concomitant medications in: (1) Placebo-controlled Phase (Weeks 0 to16), (2) Apremilast Extension Phase (Weeks 16 to 32), and (3) Observational Follow-up Phase (4 weeks).

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

9.1. Treatment Duration

Treatment duration will be summarized by treatment group for the analysis phases and for the Apremilast-exposure Period (Section 5.1). Subjects who are treated in the corresponding phases or period will be used, i.e., the safety population for Placebo-controlled Phase (Weeks 0 to 16), subjects who are treated in Apremilast Extension Phase (Weeks 16 to 32), and the apremilast subjects as treated population for the Apremilast-exposure Period.

Summary statistics for treatment duration (in weeks), as well as a frequency summary of treatment duration categories (e.g., < 4, ≥ 4 - < 8 weeks, etc.), will be provided.

9.1.1. Placebo-controlled Phase (Weeks 0 to 16)

Treatment duration (in weeks) is calculated from the date of the first dose of IP at Week 0/Visit 2 to either the date one day prior to the first dose date in the Apremilast Extension phase for the IP dispense at Week 16/Visit 7, or the date of the last dose of IP in the study for subjects who discontinue in the phase. Imputation rule for partially or completely missing last dose date is specified in Appendix A1.1.4.

Treatment duration will be summarized by actual treatment (placebo or apremilast) for the safety population.

9.1.2. Apremilast Extension Phase (Weeks 16 to 32)

Treatment duration is calculated from the first dose date in the Apremilast Extension phase for the IP dispense at Week 16/Visit 7 to the date of the last dose of IP in the study for subjects who discontinue in the phase or who complete the study at Week 32/Visit 10. Imputation rule for partially or completely missing last dose date is specified in Appendix A1.1.4.

9.1.3. Apremilast-exposure Period

Treatment duration for Apremilast-exposure Period (Section 5.1) is calculated from the date of the first dose of apremilast, which is the date of the first dose of apremilast after randomization at Week 0/Visit 2 or switched to apremilast at Week 16/Visit 7, to the last apremilast dose date for subjects who discontinue in the first 32 weeks or who complete the study at Week 32/Visit 10. Imputation rule for partially or completely missing last dose date is specified in Appendix A1.1.4.

9.2. Treatment Compliance

As part of the routine recording of the amount of IP taken by each subject, the numbers of tablets dispensed and/or returned will be recorded at visits in treatment phases. These records will be used to calculate treatment compliance.

The treatment compliance (in %) for each subject will be computed as 100 times the total number of tablets taken (the total number of tablets dispensed minus the total number of tablets returned) over the analysis phase or period divided by the intended total number of tablets that should have been taken over the same phase or period.

Summary statistics for compliance (%) will be provided by treatment arm for each analysis phase or period. Frequency summary tables of compliance will also be presented with the following categories: < 75%, ≥ 75% - ≤120%, and > 120%. A subject data listing of drug accountability records will be provided.

9.2.1. Placebo-controlled Phase (Weeks 0 to 16)

Treatment compliance will be calculated for the treatment duration in the phase specified in Section 9.1.1 and will be summarized by treatment arm for ITT population.

9.2.2. Apremilast Extension Phase (Weeks 16 to 32)

Treatment compliance will be calculated for the treatment duration in the phase specified in Section 9.1.2 and will be summarized by treatment arm for the subjects who were treated in the phase.

9.2.3. Apremilast-exposure Period

Treatment compliance will be calculated for the treatment duration in the period specified in Section 9.1.3 and will be summarized by treatment arm for apremilast as treated population.

10. PROTOCOL DEVIATIONS AND IMPORTANT PROTOCOL DEVIATIONS

Protocol deviations will be classified as protocol deviations or important protocol deviations according to Celgene or CRO's standard procedure. A list of protocol deviations and important protocol deviations for all subjects for week 16 analysis will be defined prior to the Week 16 data restriction and unblinding (i.e., prior to the unblinding of double-blind placebo-controlled phase data). The list of protocol deviations and important protocol deviations for all subjects for final analysis will be finalized prior to the final database lock. This listing of important protocol deviations for week 16 analysis will also identify which subjects are to be excluded from the per-protocol population.

Protocol deviations and important protocol deviations by treatment group and overall will be provided for the placebo-controlled phase for the ITT population, and for the Apremilast extension phase for subjects who receive at least one dose of IP during the phase. Summary tables showing the number and percent of subjects with at least one protocol deviation and important protocol deviations and by each category of protocol deviations and important protocol deviations will be provided. Listings of subjects with protocol deviations and important protocol deviations will also be provided.

11. SAFETY ANALYSIS

Safety will be assessed via descriptive statistics. Unless otherwise specified, all safety analyses described in this section will be performed for both the Placebo-controlled Phase and the Apremilast-exposure Period. The safety analyses for the Placebo-controlled Phase will be based on the safety population and presented by treatment group (placebo arm or apremilast arm), and the safety analyses for the Apremilast-exposure Period will be based on the apremilast subjects as treated population and presented by treatment group (Placebo/30 mg BID, 30 mg BID as Initiated and 30 mg BID as Treated).

For the analyses of AEs and lab marked abnormalities, the following endpoints will also be summarized:

- Subject incidence: Subject incidence (i.e., percentage [%] used in a frequency summary) is defined as the number of subjects with the specific event divided by the number of subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator.
- Exposure-adjusted incidence rate (EAIR) per 100 subject-years: The EAIR per 100 subject-years is defined as 100 times the number of subjects with the specific event divided by the total exposure time (in years) among subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator. The exposure time for a subject without the specific event is the treatment duration, whereas the exposure time for a subject with the specific event is the treatment duration up to the start date (inclusive) of the first occurrence of the specific event. The total exposure time in years is calculated by dividing the sum of exposure time in days over all subjects included in the analysis by 365.25. The EAIR per 100 subject-years is interpreted as the expected number of subjects with at least one occurrence of the specific event per 100 subject-years of exposure to the IP.

AEs and lab marked abnormalities will be summarized by subject incidence and EAIR for the Placebo-controlled Phase (Weeks 0 to 16) and for the Apremilast-exposure Period. In addition, selected summaries for the Apremilast Extension Phase (Weeks 16 to 32) and the Observational Follow-up Phase (4 weeks) may be presented if deemed necessary.

Descriptive statistics will be provided for vital signs, weight, height and BMI, laboratory values (continuous measurements) by treatment and visit, including the end of treatment visits. The baseline value, value at the time point, and change from baseline will be summarized for subjects who have values at baseline and at the time point.

Shift tables, that is, tables that summarize the baseline categories (normal, abnormal) versus the category at the end of the respective periods or versus the worst post-baseline category, include subjects who have values at baseline and at least one post-baseline value. Similarly, in frequency summaries of shifts from baseline at scheduled study weeks per protocol, only subjects who have values at baseline and at the time point will be included.

11.1. Adverse Events

AEs will be coded according to the MedDRA version 21.0 or higher. Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs presented in the standard international order and PTs within SOCs will be presented in descending order of subject incidence.

11.1.1. Overall Summary of TEAEs

An overall summary of the following TEAE categories will be provided for the Placebo-controlled Phase (Weeks 0 to 16) for subjects with:

- Any TEAE
- Any drug-related TEAE
- Any severe TEAE
- Any serious TEAE
- Any serious drug-related TEAE
- Any TEAE leading to drug interruption
- Any TEAE leading to drug withdrawal
- Any TEAE leading to death

In addition, for Apremilast Exposure Period overall summary of TEAEs will also be provided.

11.1.2. All TEAEs

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence for the Placebo-controlled Phase (Weeks 0 to 16) and the Apremilast-exposure Period.

New events of all TEAEs by exposure interval (≤ 1, > 1 to ≤ 4, > 4 to ≤ 8, > 8 to ≤ 12 and > 12 Weeks) will be summarized for the Placebo-controlled Phase. Each subject is counted once for either subject incidence or EAIR for each applicable specific TEAE in each exposure interval where an event started. The denominator of a subject incidence is the number of subjects with the exposure time reaching the lower bound of the particular exposure interval, and the denominator of an EAIR is the sum of the exposure time during the exposure interval (up to the start date [inclusive] of the first occurrence of the specific event for each subject reporting the event in the interval) among the same number of subjects as in the denominator of the corresponding subject incidence.

In addition, new events of all TEAEs by exposure interval (≤ 1, > 1 to ≤ 8, > 8 to ≤ 16, > 16 to ≤ 24, > 24 to ≤ 32, > 32 Weeks) will be summarized for the Apremilast-exposure Period.

All TEAEs will be summarized by age category (< 65, ≥ 65 years), sex, race (white vs. non-white), baseline sPGA categories (sPGA =2; sPGA =3) and, if deemed necessary, by prior/concomitant psoriasis medication usage or baseline disease characteristics.

11.1.3. Common TEAEs

TEAEs with subject incidence ≥ 5% (or another cut-off if justified) in any treatment group will be summarized by SOC and PT as well as by PT only in descending order of subject incidence.

11.1.4. Drug-related TEAEs

Drug-related TEAEs will be summarized and new events of drug-related TEAEs by exposure interval (see Section 11.1.2) will be summarized.

11.1.5. TEAEs by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, severe, and, if needed, missing; EAIR will not be provided for this summary). If a subject reports multiple occurrences of a specific event within a specific analysis phase or period, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all of the occurrences, the subject will be counted only once in the "missing" category of severity.

TEAE by maximum severity will be summarized for the Placebo-controlled Phase (Weeks 0 to 16) and Apremilast-exposure Period.

In addition, severe TEAE will be summarized for the Placebo-controlled Phase (Weeks 0 to 16), the Apremilast Extension Phase (Weeks 16 to 32), and Apremilast-exposure Period.

11.1.6. Serious TEAEs

Serious TEAEs and serious drug-related TEAEs will be summarized.

New events of serious TEAEs and serious drug-related TEAEs by exposure interval will be summarized for Placebo-controlled Phase (Weeks 0 to16).

Serious TEAEs will be summarized by age category (< 65, ≥ 65 years), sex and race.

A subject data listing of all serious AEs (both TEAEs and non-TEAEs) will be provided.

11.1.7. TEAEs Leading to Drug Interruption and Drug Withdrawal

TEAEs leading to drug interruption and TEAEs leading to drug withdrawal will be summarized.

TEAEs leading to drug withdrawal will also be summarized by age category (< 65, ≥ 65 years), sex and race.

A subject data listing of TEAEs leading to drug withdrawal will be provided.

11.1.8. Deaths

TEAEs leading to death will be summarized. A subject data listing of all deaths will be provided.

11.1.9. Onset/Duration of TEAEs for Selected PT

Onset and duration (Days) of diarrhea, nausea, headache, vomiting and tension headache will be summarized for the Placebo-controlled Phase (Weeks 0 to 16) and Apremilast-exposure Period.

11.1.10. Adverse Events of Special Interest

Summary tables and listings may be provided for the AESIs if deemed necessary.

11.2. Vital Signs and Weight

The endpoints for vital signs and weight include:

- Observed value and change from baseline over time in vital signs (temperature, pulse, and blood pressure)
- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal in pulse and blood pressure (normal ranges are defined as: 60-100 beats/minute for pulse, 90-140 mmHg for systolic blood pressure, and 60-90 mmHg for diastolic blood pressure)
- Observed value, change and percent change from baseline over time in weight

Summary statistics of observed values and changes from baseline in vital signs (including weight, for which percent change from baseline will also be summarized) will be provided over time. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal will be provided for pulse and blood pressure.

Frequency summaries of change and percent change in weight from baseline to the end of the period will be provided by baseline BMI category (< 25, ≥ 25 to < 30, ≥ 30 to < 35, ≥ 35 to < 40, and ≥ 40 kg/m^2) and by baseline weight category (< 70, ≥ 70 to < 85, ≥ 85 to < 100, and ≥ 100 kg). The categories of weight change (kg) and percent change (%) are < -20, ≥ -20 to < -10, ≥ -10 to < -5, ≥ -5 to < 0, 0, > 0 to ≤ 5, > 5 to ≤ 10, > 10 to ≤ 20, and > 20. The end-of-period or end-of-phase value is the last post-baseline value in the analysis period or phase (excluding the value obtained at the follow-up visit, if applicable) up to 28 days after the last dose of IP in the study.

A subject data listing of all vital signs and weight data will be provided.

11.3. Clinical Laboratory Evaluations

The endpoints for clinical laboratory evaluations include:

- Laboratory marked abnormalities (see Appendix A2)
- Observed value and change from baseline over time in the following laboratory parameters including but not limited to
  - Complete blood count: red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count and differential, absolute WBC counts, platelet count
  - Serum chemistry: total protein, albumin, calcium, phosphorous, glucose, total cholesterol [TC], triglycerides, high-density lipoprotein [HDL], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], uric

acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase [AST; serum glutamic-oxaloacetic transaminase, SGOT], alanine aminotransferase [ALT; serum glutamic pyruvic transaminase, SGPT], sodium, potassium, chloride, bicarbonate [carbon dioxide, CO_2], blood urea nitrogen, creatinine, lactate dehydrogenase [LDH], and magnesium
    - Dipstick urinalysis: specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocyte esterase, nitrite, and urobilinogen

- Shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal (low or high) in the above hematology and serum chemistry parameters

Summary statistics of observed values and changes from baseline in laboratory parameters will be provided over time. Frequency summaries (shift tables) of shifts from baseline to post-baseline time points and to the worst post-baseline value in terms of normal/abnormal will be provided.

Laboratory marked abnormalities will be summarized; subject incidence and EAIR for each abnormality will be calculated based on subjects with a baseline value and at least one post-baseline value for criteria requiring baseline or subjects with at least one post-baseline value for criteria not requiring baseline. A subject data listing of laboratory marked abnormalities will be provided. Laboratory marked abnormalities will also be summarized for subjects with normal values at baseline and for subjects with abnormal values at baseline separately. For the purposes of these summaries, subjects with abnormal (normal) values at baseline are defined as those whose baseline value is low (not low) for criteria concerning low values and those whose baseline value is high (not high) for criteria concerning high values; both low and high are relative to the laboratory normal range.

A subject data listing of all laboratory data, including urinalysis, will be provided.

11.4. Columbia Suicide Severity Rating Scale (C-SSRS)

All subjects will complete the Columbia-Suicide Severity Rating Scale (C-SSRS) assessment at all study visits. C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related ideations and behaviors during the assessment period (Posner, 2007). At Visit 1 (Screening) the C-SSRS will be completed for the subject's lifetime history of suicidal ideation and behavior. At all other visits the C-SSRS will be completed for ideation and behavior since the previous visit.

A summary and subject data listing of psychiatric evaluation results will be provided.

APPENDIX A1 – CONVENTIONS RELATED TO DATES

Following are the general conventions for various computations and imputations for references. Users may need to consult with study team for specific study practices or regulatory guidelines.

11.5. A1.1 Guideline of Partially Missing Date Imputation

A1.1.1 Adverse Events

Partially missing AE start dates will be imputed in the ADaM dataset for AEs, but partially missing AE end dates will not be imputed in the same dataset. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

Subjects who were treated with apremilast at Week 0/Visit 2

The principle of the imputation rules for subjects who were treated with apremilast initially is to treat the AE as treatment-emergent, i.e., occurring on or after the date of the first dose of IP, if possible.

Let an AE start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$", and the date of the first dose of IP as "$D_{IP}/M_{IP}/Y_{IP}$". The following table gives the imputation rules for partially missing AE start dates for subjects who were treated with apremilast initially.

Table 4: Imputation Rules for Partially Missing AE Start Dates for Subjects Who Were Treated with Apremilast Initially

Scenario	Condition	Imputation Rule
Partially missing date includes year only (both month and day are missing)		
1	$Y_{Event} < Y_{IP}$	$12/31/Y_{Event}$
2	Otherwise, i.e., $Y_{IP} \leq Y_{Event}$	Max (date of first dose of IP, $1/1/Y_{Event}$)
Partially missing date includes both year and month (only day is missing)		
1	$Y_{Event} < Y_{IP}$, or ($Y_{Event} = Y_{IP}$ and $M_{Event} < M_{IP}$)	Last date of M_{Event}/Y_{Event}
2	Otherwise, i.e., $Y_{IP} < Y_{Event}$, or ($Y_{IP} = Y_{Event}$ and $M_{IP} \leq M_{Event}$)	Max (date of first dose of IP, $1/M_{Event}/Y_{Event}$)

Subjects who were treated with placebo at Week 0/Visit 2

The principle of the imputation rules for subjects who were treated with placebo initially and started apremilast treatment at Week 16 is to consider the AE starting on or after the date of the first dose of apremilast, if possible; if the partially missing start date suggests that it is prior to the date of the first dose of apremilast, the AE will be considered starting on or after the date of the first dose of IP, if possible.

The following are 4 scenarios considered in the imputation rules:

1. The partially missing AE start date suggests the date is prior to the date of the first dose of IP: impute it by the latest possible date (determined by the non-missing field of the date);

2. The partially missing AE start date suggests the date is after the date of the first dose of apremilast following Week 16: impute it by the earliest possible date (determined by the non-missing field of the date);
3. The partially missing AE start date is in the same year (if both month and day are missing), or the same year/month (if only day is missing) of the first dose of apremilast following Week 16: impute it by the date of the first dose of apremilast;
4. The partially missing AE start date suggests the date is no earlier than the date of the first dose of IP but prior to the date of the first dose of apremilast following Week 16: impute it by the date of the first dose of IP, or the earliest possible date (determined by the non-missing field of the date), whichever occurs later.

Let an AE start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$", the date of the first dose of IP as "$D_{IP}/M_{IP}/Y_{IP}$", and the date of the first dose of apremilast following Week 16 as "$D_{APR}/M_{APR}/Y_{APR}$". The following table gives the imputation rules for partially missing AE start dates.

Table 5: Imputation Rules for Partially Missing AE Start Dates for Subjects Who Were Treated with Placebo Initially

Scenario	Condition	Imputation Rule
Partially missing date includes year only (both month and day are missing)		
1	$Y_{Event} < Y_{IP}$	$12/31/Y_{Event}$
2	$Y_{Event} > Y_{APR}$	$1/1/Y_{Event}$
3	$Y_{Event} = Y_{APR}$	Date of first dose of apremilast following Week 16
4	Otherwise, i.e., $Y_{IP} \leq Y_{Event} < Y_{APR}$	Max (date of first dose of IP, $1/1/Y_{Event}$)
Partially missing date includes both year and month (only day is missing)		
1	$Y_{Event} < Y_{IP}$, or ($Y_{Event} = Y_{IP}$ and $M_{Event} < M_{IP}$)	Last date of M_{Event}/Y_{Event}
2	$Y_{Event} > Y_{APR}$, or ($Y_{Event} = Y_{APR}$ and $M_{Event} > M_{APR}$)	$1/M_{Event}/Y_{Event}$
3	$Y_{Event} = Y_{APR}$ and $M_{Event} = M_{APR}$	Date of first dose of apremilast following Week 16
4	Otherwise, i.e., $Y_{IP} < Y_{Event} < Y_{APR}$, or ($Y_{IP} = Y_{Event} < Y_{APR}$ and $M_{IP} \leq M_{Event}$), or ($Y_{IP} = Y_{Event} = Y_{APR}$ and $M_{IP} \leq M_{Event} < M_{APR}$), or ($Y_{IP} < Y_{Event} = Y_{APR}$ and $M_{Event} < M_{APR}$)	Max (date of first dose of IP, $1/M_{Event}/Y_{Event}$)

A1.1.2 Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset for prior/concomitant medications/procedures. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date. If the imputed start date is after the stop date, the start date will be imputed as the stop date – 1.

A.1.1.3 Medical History

Partially missing medical history start dates will be imputed in the ADaM dataset for medical history (for the purposes of calculating durations of PsA and psoriasis). The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

If the imputed start date is after the stop date, the start date will be imputed as the stop date – 1.

A1.1.4 Treatment Duration

Partially or completely missing last dose dates will be imputed in the ADaM dataset for treatment duration.

When partially missing last dose date is available, set last dose date to the maximum of [the earliest possible date given the non-missing field(s) of last dose date, the minimum of (the latest possible date given the non-missing field(s) of last dose date, last known date in database, first non-missing Early Termination (ET) visit date)]

When last dose date is completely missing, set last dose date to the minimum of (last known date in database, first non-missing Early Termination (ET) visit date)

Last known date in database is defined as maximum of (last visit date, lab, vital signs, ECG assessment date, AE start or end dates, concomitant medications start or end dates, concomitant procedure date, last dose date from 'Disposition- Treatment' page, treatment exposure start or end dates where doses were completely or partially taken, death date).

APPENDIX A2 – LABORATORY MARKED ABNORMALITIES CRITERIA

Table 6: Laboratory Marked Abnormalities Criteria

Category / Analyte	**SI Units**	**Criteria**
Chemistry/ Alanine Aminotransferase (SGPT)	U/L	> 2*ULN
Albumin	Kg/m3	< 25
Alkaline Phosphatase	U/L	> 400
Aspartate Aminotransferase (SGOT)	U/L	> 2*ULN
Total Bilirubin	µmol/L	> 2*ULN
Total Bilirubin and Alanine Aminotransferase /Aspartate Aminotransferase	µmol/L and U/L	Bilirubin Value > 2xULN with (ALT or AST value > 2xULN)
Blood Urea Nitrogen	mmol/L	> 24
Calcium	mmol/L	< 1.8 > 3.0
Cholesterol	mmol/L	> 7.8
Creatinine	µmol/L	> 1.5*ULN
Glucose	mmol/L	< 2.8 > 13.9
Hemoglobin A1C	%	> 6.5
Lactate Dehydrogenase (LDH)	U/L	> 2*ULN
Magnesium	mmol/L	> 1.2
Phosphate	mmol/L	<1.03 >1.94
Potassium	mmol/L	<3.0 >5.4
Sodium	mmol/L	<132 >147
Triglycerides	mmol/L	> 3.4

Urate	umol/L	Male: > 480 Female: > 480
Hematology/ Hemoglobin	g/L	Female <110, Male <110 Female >150, Male >150
Leukocytes	10^9/L	< 2.0
Lymphocytes	10^9/L	< 1.0
Neutrophils	10^9/L	< 1.5
Platelets	10^9/L	<100 >500

APPENDIX A3– REPORTING CONVENTIONS

- Statistical test of the treatment difference will use two-sided significance level 0.05 for significance or nominal significance.
- P-values will be rounded to 4 decimal places. p-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999';
- Confidence intervals (CIs) will be presented as two-sided 95% CIs unless specified differently in specific analysis;
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, the sample size, mean, median, standard deviation (SD), minimum, and maximum for continuous variables, the 25th (Q1) and 75th (Q3) percentiles will also be applied to efficacy continuous variables;
- Mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value;
- Percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses;
- Analysis and summary tables will have the analysis population sample size (i.e., number of subjects) in the column header;
- Subject data listings will be provided to support the tables and graphs. Listings will be sorted for presentation in order of subject number and date of procedure or event.